SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Clinical observations on the treatment of osteoporosis and fracture risk in patients with psoriatic arthritis

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The PhD Defense takes place at the University of Debrecen, Faculty of Medicine, Department of Internal Medicine, Lecture Hall of Building A, June 17, 2025. at 1:30 pm.

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1. INTRODUCTION: the importance of osteoporosis, presentation of the topic

Osteoporosis (OP) is a disease affecting the entire skeletal system, which affects approximately 200 million people worldwide, making it one of the greatest public health problems. The importance of this topic is underscored by data from 2019, which indicate that 5.6% of the European population over the age of 50 is affected; this translates to approximately 25.5 million women and 6.5 million men.

Osteoporosis, as a widespread disease, places a tremendous economic burden on society globally. In Europe, the healthcare burden caused by OP surpasses that of malignant tumors (with the exception of lung cancers) and is comparable to the burden caused by rheumatoid arthritis, asthma, or hypertension-related heart diseases. Financially, in 2013, osteoporosis-related costs amounted to 37 billion euros in the European Union, with fractures accounting for a significant portion (66%) of this expense. OP is a highly underdiagnosed disease, with estimates suggesting that only one-third of the frequent vertebral fractures are identified. Additionally, literature shows that nearly 80% of patients who have already suffered an OP-related fracture and are at high risk of future fractures do not receive anti-osteoporotic therapy and are not even diagnosed.

It is a well-known fact that the global population is aging rapidly. Analyzing population data in 2010, it was estimated that 158 million people belonged to high fracture risk group. Based on demographic trends, this number is expected to double by 2040.

Fractures typically caused by OP are hip, vertebral, distal forearm, and proximal upper arm fractures, of which hip and vertebral fractures significantly increase mortality. In 2010, 3.5 million fractures were recorded in the European Union: of these, 610,000 were hip fractures, 520,000 vertebral fractures, 560,000 forearm fractures and 1.8 million other fractures (e.g. pelvis, rib, sternum, fibula). Two-thirds of all fractures were suffered by the female population. Based on demographic trends, this 3.5 million fracture count is projected to rise to 4.5 million by 2025.

Hip fractures have the highest morbidity rates. Half of the patients who lived independently before the fracture will require long-term care afterward. In England, 79,000 hip fractures were registered in 2010, with a cost of £3.5 billion, which is expected to rise to £5.5 billion by 2025. Globally, there was a nearly 25% increase in hip fractures between 1990 and 2000. The number of fractures peaked in both sexes in the 75-79 age group, while other fractures were most common between ages 50-59, then declined somewhat with age. Current estimates suggest that by 2050, the incidence of hip fractures will increase by 310% in men and 240% in women compared to the incidence recorded in 1990.

In 5-10% of patients, the first hip fracture is followed by another; 23% of subsequent fractures will occur within the first year after the initial fracture, and 70% will occur within five years. Hip fractures are clearly associated with chronic pain, reduced mobility, and a continuous decline in the ability to live independently. Alarming statistics illustrate the consequences of hip fractures. In the first year following the fracture, mortality rates reach 20-24%, and the elevated risk of death can persist for up to 10 years. Mortality and morbidity rates are twice as high in men compared to women. 40% of patients become unable to walk independently after the

fracture, and this number rises to 60% after another year. Additionally, 33% of patients become incapable of self-care in the first year after the fracture. The importance of so-called sentinel fractures is indicated by the fact that more than 55% of those who suffered a hip fracture had a previous vertebral fracture.

According to the EVOS study, which analyzed vertebral fracture data, the prevalence of fractures in the 50-79 age group in Europe is around 12%, and this increases with age in both sexes. In women, the rate is 3% under age 60 and 19% over age 70; in men, it is 7.5% and 20%, respectively. However, these figures may be underestimated, as many vertebral fractures are asymptomatic, known as morphometric fractures, and thus go undiagnosed. The frequency of vertebral fractures is highlighted by a study showing that a vertebral fracture occurs every 22 seconds worldwide.

Several studies have confirmed that vertebral fractures increase the risk of other fractures as well. Patients who have experienced a vertebral fracture are at a significantly higher risk of suffering additional fractures. The relative risk of subsequent fractures is 6.5 times higher for men and 2.5 times higher for women, with most occurring within two years. These fractures also lead to a decline in quality of life. Various questionnaires have shown that as the number of vertebral fractures increases, the quality of life proportionally decreases. Vertebral fractures also greatly influence mortality, increasing age-adjusted mortality risk by eightfold. According to a study based on the General Practice Research Database (GPRD) in England, 12-month survival following a vertebral fracture was 86.5% in women, while 5-year survival was 56.5%. Mortality following both vertebral and hip fractures is significantly affected by the presence and severity of comorbidities.

The GLOW study confirmed that high blood pressure, heart disease, and asthma bronchiale, COPD, arthritis, stroke, inflammatory bowel diseases, Parkinson's disease, multiple sclerosis, type 1 diabetes mellitus all increase the fracture risk. A German study examining 20,000 adults found that 95% of osteoporosis patients had some form of comorbidity.

Among the conditions that negatively affect bone density is psoriasis, as well as the closely related psoriatic arthritis. The exact relationship between these conditions and osteoporosis is still not fully understood.

The data detailed above clearly highlight the importance of early detection of osteoporosis and the prompt initiation of adequate therapy in order to prevent as many fractures with serious consequences as possible.

In this context, we conducted research in two areas:

1. Tight control as a new therapeutic strategy in the treatment of osteoporosis.
2. The relationship between the disease-specific characteristics of psoriatic arthritis and osteoporosis, fractures, and falls

2. TIGHT CONTROL: A NEW THERAPEUTIC STRATEGY IN THE MANAGEMENT OF OSTEOPOROTIS

2.1. Literature review

2.1.1. Definition of Osteoporosis

Osteoporosis is the most common metabolic bone disease. It is a progressive, systemic disorder that results in the deterioration of bone microarchitecture, a decrease in mineral content, and consequently an increase in bone fragility and fracture risk. According to the WHO definition, osteoporosis is diagnosed when bone mineral density (BMD) is at least 2.5 standard deviations (SD) below the average for young adult women, meaning the T-score is equal to or lower than -2.5.

Osteoporosis is a multifactorial condition influenced by genetic, environmental, and lifestyle factors. Its basis can be seen as a shift in the balance of bone remodelling in the direction of resorption. Bone remodelling takes place until our death, and its function is to repair microfractures, preserve the integrity of the skeleton, and maintain mineral homeostasis.

When the balance in this strictly regulated and complex remodelling process is disrupted and resorption becomes dominant, bone loss and eventually osteoporosis can develop. Osteoporosis can be classified as primary or secondary, depending on whether it is associated with another underlying disease. Many conditions can lead to systemic bone loss and secondary osteoporosis. 30% of women and 60% of men with osteoporosis have secondary osteoporosis. The two main forms of primary osteoporosis are postmenopausal and senile osteoporosis, but it also includes juvenile and idiopathic male osteoporosis.

Postmenopausal osteoporosis primarily results from a decrease in estrogen levels, leading to the loss of estrogen's bone-protective effects. Postmenopausal osteoporosis predominantly affects trabecular bone, which has a higher turnover rate. As a result, bones rich in trabecular tissue, such as the distal radius and vertebrae, are particularly vulnerable to fractures.

Bone loss occurs at a rapid pace immediately following menopause. This accelerated bone loss begins during the year preceding menopause and continues for approximately 3-5 years after menopause. During this period, the rate of BMD loss can reach up to 10% per year. After this initial period, the rate of bone loss slows down and eventually stabilizes at levels seen in senile osteoporosis.

Senile OP is a disease of women and men over 75 years of age. Several mechanisms are involved in its formation. Oxidative stress that increases with age antagonizes the Wnt signaling pathway, thereby inhibiting bone formation; a decrease in the level of IGF-1 (Insulin-like growth factor 1) inhibits osteoblast functions. Bone loss is further exacerbated by low estrogen levels (in both sexes); chronic vitamin D deficiency, which leads to secondary hyperparathyroidism and increased resorption activity. Both trabecular and cortical bone are affected and the frequency of hip fractures also increases.

The development of secondary OP can be caused by many pathologies and conditions. Among them are many drugs (steroids, antiepileptics), endocrine diseases (hyperparathyroidism, thyrotoxicosis, diabetes mellitus, Cushing 's syndrome), gastrointestinal diseases (malabsorption, inflammatory bowel diseases), hematological diseases (leukemia, multiple myeloma), neurological abnormalities (Parkinson's disease, sclerosis multiplex,

epilepsy), autoimmune diseases (rheumatoid arthritis, spondylitis ankylopoetica, systemic lupus erythematosus), and many other factors (AIDS, end-stage renal failure, COPD, etc.) can contribute.

The most common type of secondary osteoporosis is glucocorticoid-induced osteoporosis. In this condition, elevated levels of glucocorticoids, exceeding physiological concentrations, inhibit osteoblast differentiation and function, while promoting osteoclast activity through increased RANKL and RANK expression. Glucocorticoids also reduce intestinal calcium reabsorption, increase renal calcium excretion, and negatively affect estrogen production. Additionally, glucocorticoid therapy can lead to functional vitamin D3 deficiency by reducing vitamin D receptor expression. Oral glucocorticoids induce rapid bone loss and increase fracture risk (particularly for vertebral fractures) in a dose-dependent manner within 3-6 months. Given that an estimated 1-2% of the population is on long-term steroid therapy, it is crucial to initiate bone-protective therapy as soon as possible. While fracture risk increases quickly, it tends to slow down over time, and decreases after discontinuation of glucocorticoid therapy. Studies have shown that fractures in steroid users occur at higher BMD levels compared to non-steroid users, likely due to deteriorated bone quality and increased fall risk. This elevated fall risk is associated with glucocorticoid-induced sarcopenia, immobility, and reduced effectiveness of fall prevention mechanisms.

The prolonged high levels of thyroid hormones, as seen in thyrotoxicosis, can also lead to secondary osteoporosis. This condition is characterized by increased bone formation and increased bone resorption simultaneously. Thyrotoxicosis accelerates the turnover rate, reducing the duration of remodeling cycles, disrupting coupling, and leading to an imbalance with increased resorptive activity. This imbalance can result in bone loss of up to 10% per year as well.

Due to their prevalence, it is also important to highlight the role of inflammatory autoimmune diseases in causing osteoporosis. We will discuss these in more detail later.

2.1.2. Osteoporosis risk factors, fracture risk factors

Several diseases and conditions predispose to the development of osteoporosis. These include female gender, advanced age, caucasian race, low BMI (body mass index), family history of osteoporosis, low calcium intake, early menopause, heavy alcohol consumption (more than 3 units/day), smoking, immobility. Certain medical conditions also promote the development of osteoporosis as it has already mentioned , such as hypogonadism, hypercorticism, hyper- and hypothyroidism, renal hypercalciuria, kidney failure, malabsorption, diabetes mellitus, cancers (e.g., multiple myeloma), autoimmune diseases (e.g., rheumatoid arthritis, spondyloarthritis, dermatomyositis/polymyositis), and the use of certain medications (e.g., steroids, anticoagulants, anti-estrogens/anti-androgens, thiazolidinediones, proton pump inhibitors).

Risk factors for osteoporosis overlap somewhat with fracture risk factors. Common factors include advanced age and immobility. Additional fracture risk factors include a previous fracture, a family history of hip fractures, low BMD, high resorptive marker levels, frequent falls, balance disorders, vision impairments, a fall-prone environment, dementia, the use of certain medications (e.g., sedatives, antidepressants, neuroleptics, orthostatic agents), and a long femoral neck.

The importance of fracture risk assessment

In the last decade, it has become increasingly evident that factors other than BMD are also responsible for the occurrence of low-energy fractures. Almost half of the fractures occur in non-osteoporotic patients. This realization led to the development of clinical risk assessment, which allows more accurate selection of patients in need of treatment.

Various tools are used to estimate fracture risk, but the most widely used is FRAX (Fracture Assessment Tool), which has gained popularity due to its online accessibility (http://www.shef.ac.uk/FRAX). The original FRAX model, introduced in 2008, calculates the 10-year cumulative risk of major osteoporotic fractures (hip, spine, forearm, shoulder) based on eleven clinical risk factors, with or without knowledge of femoral neck BMD. The fundamental principle is that a patient who has sustained a fracture from minimal trauma is considered at high risk, and thus, pharmacological therapy should be initiated without further consideration. For patients who have not yet sustained a fracture, the decision to initiate pharmacological therapy should be based on the FRAX assessment. FRAX calculates fracture risk using the following factors: age, sex, previous osteoporotic fracture, BMI, parental hip fracture, steroid use, BMD measured at the femoral neck or hip, smoking, RA, secondary osteoporosis, alcohol consumption of more than 3 units/day.

Specific antiporotic treatment is generally required by patients whose calculated fracture risk falls above the so-called intervention threshold. In our country, a fixed intervention threshold is used, which for cost-effectiveness reasons was set at 3% for hip fracture risk and 20% for other major fractures (vertebrae, wrist, upper arm).

A major advantage of FRAX is that it can be used without bone density measurement, which is especially useful in countries where DEXA examination is only limited or not available at all. It is also important to note that the original FRAX version does not account for all factors that may influence fracture risk. For example, after an initial sentinel fracture, the risk of a subsequent fracture remains exceptionally high for about 2 years ("imminent risk"), and then gradually decreases over time. Accordingly, correction options have been developed for several such factors.

In general, it is recommended to routinely assess fracture risk in women over 65 and men over 75 who have not yet experienced a fracture, except in cases where anti-osteoporotic therapy is not feasible due to a very short life expectancy or comorbid conditions that exclude medication.

2.1.3. The importance of therapeutic discipline

In the treatment of osteoporosis, there are increasingly effective medications available, but the efficacy of therapy is fundamentally influenced by whether patients consistently adhere to the prescribed treatment. The therapeutic discipline (adherence) of osteoporotic patients is among the lowest, as overall half of the patients take the antiporotic drugs as prescribed, and 47% stop the therapy within 6 months. Decreased adherence leads to treatment inefficiency and increases healthcare costs, morbidity and mortality.

Adherence is influenced by two factors. One is compliance, which is characterized by what percentage of the prescribed dose the patient takes in a given time. The most common feature of this is MPR (Medication Possession Ratio), which shows how much of the prescribed medication the patient has taken. The other is

persistence, which indicates how long the patient continues to take the medication (regardless of compliance). Together and separately, these factors significantly influence the effectiveness of antiporotic treatments.

Studies have shown that osteoporosis patients often exhibit poor adherence: approximately 20% of patients do not pick up their prescribed bisphosphonates, and more than 50% of patients fail to follow long-term treatment instructions. In a study involving nearly 60,000 patients, less than 25% demonstrated adequate compliance one year after the prescription of anti-osteoporotic medication.

A large study conducted in England found that persistence decreased over time: six months after starting therapy, 56% of patients persisted, compared to 31% after 24 months, and only 13% after 5 years. Persistence was also examined in relation to the antiporotic drugs used: after 24 months, 50% of the patients receiving denosumab, per os 19% of patients taking bisphosphonates, parenteral 15% of bisphosphonate patients continued therapy. Overall, they found that persistence was lowest with teriparatide and most favorable with denosumab.

Compliance it also significantly affects BMD and fracture frequency. Eastell et al showed a significant correlation between the number of bisphosphonate doses taken and L-spine BMD changes during a one-year follow-up period. According to British registry data, patients with adequate compliance had a 16% lower fracture risk in a study evaluating bisphosphonates. A large retrospective study involving 685 505 patients starting anti-osteoporotic therapy revealed that nonadherent patients had a 20% higher chance of experiencing any fracture over a 7-year follow-up period compared to adherent patients. Additionally, the medical costs for nonadherent patients were 13% higher than those for adherent patients.

2.2. Objectives

In our study, we sought to answer the following questions:

1. Is there a difference in treatment effectiveness between patients under tight control (those who attend specialist clinics every 3 months and are treated based on BTM levels) and those in the routine control group (patients who are monitored annually without bone marker level monitoring)?
2. During the follow-up period, how often did medication changes involve switching between drugs with the same mechanism of action versus switching to drugs with different mechanisms of action?
3. Does the application of the tight control principle influence the patients' therapeutic adherence?

2.3. Patients and methods

Our self-initiated scientific follow-up study was conducted with the participation of 224 patients cared for at the rheumatology department of the Rheumatology and Immunology Clinic, Kenézy Gyula Campus of the Clinical Center of the University of Debrecen.

The study included patients newly diagnosed with primary osteoporosis, aged between 40 and 95 years, who provided written informed consent.

Patients were excluded from the study if they had a history of malignant tumors or other conditions affecting bone density (such as rheumatoid arthritis, hyperthyroidism, hypothyroidism, renal failure, malabsorption syndrome, primary hyperparathyroidism, alcoholism), or if they were undergoing long-term

medication that influences bone metabolism (such as steroids, thiazides, proton pump inhibitors, thyroid hormones, anticoagulants, antiepileptics, glitazones).

For patients meeting the inclusion criteria, a detailed medical history was taken, during which age, gender, BMI, important comorbidities such as ischemic heart disease, hypertension, diabetes mellitus, hypercholesterolemia, etc. were recorded; and we recorded the anamnestic number of osteoporotic fractures. The data collection was followed by a physical examination. Finally, a laboratory examination was performed, with particular attention to the parameters of bone metabolism: calcium, alkaline phosphatase, osteocalcin (OC), CTX-I, TSH and parathormone. The OC, CTX-I and PTH levels were measured from a morning blood sample taken on an empty stomach and were determined using an electro -chemiluminescence immunochemical assay (ECLIA). The inter-assay variation coefficient for PTH is <7% (normal range 0.127 pmol /L-530 pmol /L), for OC <4% (normal range 0.5 µg /L-300 µg /L), for CTX was <7% (normal value 0.010 µg /L-6 µg /L). The BTM levels obtained in this way were considered normal if they fell within the normal range corresponding to age and gender.

Finally, all patients in care underwent an AP-directional DEXA scan of the left femoral neck and the lumbar spine (L. I.-L. IV. segments). As a standard therapy, every patient received at least 1000 IU of vitamin D3 and 800 mg of calcium, while the specific anti-osteoporotic therapy was decided by the treating physician based on the professional guidelines in effect at the time of the study.

The study participants were randomly divided into the following two groups:

Tight control group

Patients in this group met with their treating physician every three months at the outpatient clinic. Each visit included checking bone turnover marker (BTM) levels, discussing medication adherence, and emphasizing the importance of precise therapy adherence.

Starting from the second time, the attending physician could use the following options based on the laboratory results:

1) If the PTH and CTX-1 values were in the normal range or decreased compared to the initial level, the patient could be scheduled for the next follow-up appointment in 3 months without altering the therapy
2) If any of the marker levels showed an increase compared to the initial values, the attending physician could:
    a) remind the patient again to follow the therapeutic instructions exactly
    b) increase the dosage of vitamin D_3 and/or calcium
    c) suggest a different form of calcium intake
    d) change the oral antiporotic medication to an intravenous form of the same active ingredient
    e) switch to another antiporotic agent from the same or a different pharmacological class

Routine treatment group

The patients included in this group appeared annually at our outpatient clinic and, accordingly, continued the calcium, vitamin D3 and specific antiporotic therapy started at their first visit during the average follow-up period of one year.

After the follow-up period, the patients of both groups underwent a DEXA examination again, and their attending physician questioned them about the fractures that occurred during the follow-up period, and inquired about the accuracy of their medication adherence, and noted any missed doses and their duration. Patients' compliance was assessed as adequate if at least 80% of the prescribed medication was taken.

Statistical analysis

The collected data were statistically analyzed with IBM SPSS Statistics 22.0 (Armonk, NY: IBM Corp.). Our null hypothesis was that during the follow-up period, patients treated according to tight control will have a greater BMD increase and fewer fractures, as well as higher compliance, compared to those receiving routine treatment.

We divided the patients into two groups based on the frequency of outpatient visits (3 months vs. 12 months). The absolute (BMD2 - BMD1) and relative (BMD2 / BMD1) changes in BMD were calculated from the DEXA scan results performed at the start and end of the study.

The normality of the data was tested using the Shapiro-Wilk test. Data from groups that did not follow the normal distribution were compared using the Mann- Whitney test. Since the two groups differed in patient age and follow-up time, we used a general linear model to examine the effects of age, time between DEXA scans, and frequency of outpatient visits on BMD changes. We excluded patients whose follow-up time between two DEXA scans exceeded 24 months, as this significantly affected the analysis results. After this exclusion, the follow-up time was not significantly different between the two groups.

Due to possible therapeutic inhomogeneity, the analysis of the data was repeated after the exclusion of patients treated with raloxifene, at which time all patients received bisphosphonate therapy uniformly. The results of the repeated analysis did not differ from the first.

We considered results statistically significant if the p-value was less than 0.05.

2.4. Results

A total of 224 patients participated in the study. Of these, 111 patients (103 women and 8 men) were included in the tight control group, whose average age was 71.18 years, while their average BMI was 30.11 kg/m^2. At the initial clinic visit, most patients were started on bisphosphonate therapy: 76 cases received alendronate, 17 received risedronate, 10 received ibandronate (8 oral and 2 parenteral), and 8 received raloxifene. The average follow-up period for this group was 14 months.

During this period, there were 18 instances of therapy changes: 8 times to a medication from a different pharmacological group, 10 times within the same class of drugs, and two patients had their therapy modified twice. Of the 111 patients, 79 had a history of osteoporotic fractures, with 2 vertebral and 1 peripheral (proximal humerus) fractures occurring during the follow-up period. The median DEXA results at the beginning of the follow-up period were 0.842 g/cm² for the lumbar spine and 0.745 g/cm² for the femoral neck; at the end of the

follow-up period, the median values were 0.881 g/cm² for the lumbar spine and 0.749 g/cm² for the femoral neck. The proportion of patients with adequate compliance was 82% for anti-osteoporotic medication, 78.4% for calcium, and 85.5% for vitamin D3.

In the routine treatment group, we analyzed data from 113 patients, comprising 11 men and 102 women. The average age was 74.42 years, and the average BMI was 29.53 kg/m². The therapy was initiated as follows: 89 patients received alendronate, 21 received risedronate, and 3 received zoledronate. There were no changes in therapy during the study period, which had an average follow-up duration of 14.59 months.

68 patients had a history of fracture, and 2 vertebral and 2 peripheral fractures were newly recorded. The median values of the DEXA results at the beginning of the follow-up period were 0.903 g/cm^2 on the lumbar spine and 0.742 g/cm^2 on the femoral neck ; and at the end of the follow-up period, it was 0.915 g/cm ^{2} on the lumbar spine and 0.72 g/cm^2 on the femoral neck . Adequate compliance was found in 67.2% of patients with antiporotic, 61% with calcium and 65.5% with vitamin D3.

Due to the small number of fractures that occurred during the study, we could not perform a statistical analysis.

Bone density changes

The number of patients experiencing BMD gain and loss was similar in the two groups. The difference between the results of the two treatment groups was not significant either with respect to the relative or the absolute difference with the Mann- Whitney test.

In analyzing the BMD changes measured at the femoral neck, we found that a greater number of patients achieved BMD increase in the tight control group compared to the routine treatment group. Comparing the data from the two groups using the Mann-Whitney test, the difference was statistically significant, and this significance was observed whether we analyzed absolute BMD changes or relative BMD changes.

Given that there were 8 raloxifene users among those in the tight control group, and this increases the inhomogeneity of the therapy and may affect the result, we therefore repeated the data analysis without the data of patients receiving raloxifene. Even then, we obtained similar results, despite the smaller number of patients, the difference between the results of the two groups was even more pronounced. For the difference measured in the absolute change of BMD of the femoral neck, p=0.025 and for the difference measured in the relative change, p=0.023 values were obtained using the Mann- Whitney test.

Compliance

In the tight control group, a higher percentage of patients adhered to their therapy with at least 80% compliance for both the anti-osteoporotic medication, as well as for D3 vitamin and calcium. In the routine treatment group, 67.2% of patients adhered properly to their anti-osteoporotic medication, compared to 82% in the close monitoring group. For D3 vitamin and calcium, the percentage of compliant patients was 65.5% and 61% in the routine treatment group, respectively, whereas in the closemonitoring group, it was 85.5% and 78.4%.

2.5. Discussion

In recent decades, the therapeutic arsenal of osteoporosis has been expanding, we have more and more options and more and more effective drugs to reduce the risk of fractures. According to the data of large multicenter studies, all currently avaible treatments on the market are effective for the treatment of osteoporosis with adequate calcium and vitamin D_3 supplementation. However, real-world data show less favorable outcomes, as antiporotic medications only achieve their intended effects when patients adhere to the prescribed therapy.

In practice, the persistence and adherence of osteoporosis patients are often far from optimal. Of these, patient persistence appears to be the weakest link. While therapeutic compliance is crucial, the challenge lies in maintaining long-term adherence to prescribed treatments. This study aimed to assess whether more frequent follow-ups with tighter control could improve these outcomes compared to routine care.

In a Hungarian study, they processed the data of 296 300 patients and found that the one-year persistence rate was 81% among those receiving denosumab, 21% among those receiving daily ibandronate, 34% for weekly ibandronate, and 27% for monthly ibandronate. Persistence was higher (57%) in the case of the quarterly intravenous form. The same study also found that patients with at least 80% compliance had a 23% lower risk of fractures, a 28% reduction in hospital admissions due to fractures, and a 43% decrease in mortality. These findings emphasize the critical importance of therapeutic adherence. Various strategies have been attempted to improve adherence, including patient education, reducing dosing intervals, and using parenteral administration. These approaches have had varying degrees of success in enhancing adherence and/or compliance.

However, the physician's personality and the "doctor-medicine" effect are factors that may be equally important. Many professional organizations recommend considering the principle of close monitoring in developing treatment strategies for inflammatory joint diseases, as outlined in the EULAR guidelines for rheumatoid arthritis and psoriatic arthritis. Numerous studies have demonstrated the positive predictive value of decreases in bone turnover markers (BTMs) for the effectiveness of antiresorptive therapy, and there is evidence suggesting that periodic BTM monitoring can improve therapeutic compliance. Data from US indicate that regular monitoring of BTM levels often leads to more frequent therapy adjustments and reduces patients' fracture risk. This underscores the importance of integrating comprehensive monitoring strategies into treatment plans to optimize outcomes and adherence. By ensuring that patients' responses to therapy are regularly assessed and appropriately managed, healthcare providers can significantly enhance the effectiveness of osteoporosis treatments.

It is also worth being aware that bone turnover markers are not suitable for establishing a diagnosis of osteoporosis, but their elevated level can mean accelerated bone loss. According to some studies, higher bone turnover marker levels are associated with increased fracture risk, independent of BMD. According to several authors, BTM monitoring of women around menopause may be suitable for identifying rapid bone loss individuals, who are likely to develop osteoporosis in the coming years.

Moreover, resorptive markers can also indicate therapeutic response to bisphosphonates, as these markers typically decrease by 25-30% during the first 6 months of oral bisphosphonate therapy. Monitoring BTM levels during a bisphosphonate treatment hiatus (drug holiday) could be useful in determining when to resume

bisphosphonate therapy, although large-scale clinical studies on this topic are still lacking. Currently, several guidelines recommend using serum CTX-I and serum PINP levels for monitoring antiresorptive therapy. These markers can also be used to detect poor patient adherence.

Based on our findings, it can be concluded that although the most common practice due to healthcare system overload is for patients to attend outpatient clinics only annually and for their primary care physicians to manage their care between visits, the principles of close monitoring should still be considered. This approach may lead to greater BMD gains and higher therapeutic adherence.

Possible limitations must be taken into account in order to evaluate the results of our present study. The difference in BMD gain in the two groups only slightly exceeded the significance limit. The sample size was not large, and there were significant differences in the types of antiosteoporotic medications used between the two groups. Nevertheless, as this was an observational study, our results may better reflect real-life data compared to double-blind, placebo-controlled trials.

3. RELATIONSHIP OF DISEASE-SPECIFIC CHARACTERISTICS OF PSORIATIC ARTHRITIS WITH OSTEOPOROSIS, FRACTURES AND FALLS

3.1. Literature review

3.1.1. Psoriatic arthritis definition, pathomechanism, correlation with skin symptoms

Psoriasis is one of the most common dermatological immunomediated conditions, involving dysfunctions of both the innate and adaptive immune systems. Its prevalence in Europe ranges from 0.73% to 2.90% of the general population. There is no significant gender difference, and symptoms can appear at any age, although the most common onset occurs between 18-39 years and 50-69 years. According to Henseler and Christophers, the condition is divided into two subtypes based on the age of onset: early onset (Type I) for those under 40 years of age, and late onset (Type II) for those over 40 years. Most patients fall into the Type I category, which is characterized by familial clustering and association with the HLA-Cw6 antigen, whereas these features are not observed in Type II psoriasis.

Psoriasis is a clinically heterogeneous disease, with the most common form (90%) being chronic plaque psoriasis (psoriasis vulgaris). This typically presents on the extensor surfaces of the limbs, the trunk, the scalp, and the sacral region. It is characterized by symmetrical, well-defined plaques covered with grayish-white scales, which may be itchy and painful in some cases. Less common is guttate psoriasis, which appears as papules 2-10 mm in diameter distributed across the body, particularly on the trunk and proximal parts of the limbs. A special form is inverse psoriasis, which causes non-scaling, red, shiny plaques in skin folds. The rarest form is erythrodermic psoriasis, where the entire or nearly the entire skin surface is affected, resulting in hyperemic, infiltrated, and peeling skin. This can be life-threatening and is often associated with general symptoms such as fever, subfebrility, hypoalbuminemia, often anemia, and sometimes a hypercatabolic state. Psoriasis may also present in pustular form, which can be generalized or confined to the palms and soles. Some consider pustular psoriasis as a separate condition.

Psoriasis affects the nails in 5-50% of cases, often causing pain and presenting a challenging condition

to treat. In 1-5% of patients with nail involvement, there are no distinct skin symptoms, making the diagnosis of nail psoriasis often difficult.

Among the comorbidities associated with psoriasis, the most common is psoriatic arthritis (PsA). It is expected to develop in about one-third of psoriasis patients, with a prevalence of 0.3-1% in the general population.

In most cases (80%), psoriasis precedes the onset of arthritis. Less frequently (5-10%), arthritis appears before psoriasis, and in approximately 10% of cases, arthritis and psoriasis occur simultaneously. Several risk factors for the development of PsA have been described, with current consensus indicating that the highest risk is associated with obesity, involvement of the scalp, nails, and skin folds in psoriasis, and a family history of PsA. Interestingly, among psoriasis patients with only skin symptoms, nails are affected in 1-50% of cases, whereas in PsA, this rate exceeds 80%. It has been shown that PsA, particularly its form with distal interphalangeal (DIP) joint involvement, is more closely associated with nail involvement than with skin psoriasis symptoms. The likelihood of developing PsA is increased by certain HLA and other genes (HLA-B13, B-17, B-27, B-38, B-39, HLA-Cw6 antigens, the MICA-9 gene, TNF-α/c1d3, the CARD-15 gene, and some IL-23 gene polymorphisms). Certain genes are also associated with the type of disease (e.g., DR4-polyarthritis, B27-sacroiliitis) and its outcome (e.g., DR4, TNF-α-309-erosivity).

The pathogenesis of PsA is complex; beyond genetic predisposition, it is influenced by epigenetic modifications of DNA (such as methylation), changes in the gut microbiome, biomechanical stress, altered cytokine environments related to obesity, and bacterial (Streptococcus) infections of the upper respiratory tract, all of which increase the risk of disease development.

The fundamental pathogenetic mechanisms of PsA occur in the skin, where unknown factors that damage the epithelium trigger the activation of epidermal cells (keratinocytes). These activated keratinocytes produce antimicrobial peptides (LL37, beta-defensin, S100A7, S100A15) that form complexes with self-antigens released due to "damage." These complexes activate plasmacytoid dendritic cells, which in turn produce IF-α to activate myeloid dendritic cells and keratinocytes. The activated keratinocytes secrete IL-1β, TNF-α, and IL-6, while myeloid dendritic cells mainly produce TNF-α, IL-23, IL-12, and IL-6. Activated dendritic cells migrate to nearby lymph nodes, where they activate naive T cells, which differentiate into various effector cell types (Th1, Th17, Th22) depending on the cytokine environment.

The differentiation into Th1 cells is promoted by IL-12 produced by myeloid cells, Th22 production is influenced by TNF-α and IL-6, while Th17 activation is supported by IL-1 and IL-6 in the presence of TGF-β. These Th17 cells survive and become activated in the presence of IL-23 produced by dendritic cells. Th1 cells are characterized by the production of IFN-γ, IL-2, and TNF-α; Th17 cells produce IL-17A, IL-17F, and IL-22; and Th22 cells produce IL-22. The influx of these cells and the cytokines they produce into the joints and surrounding structures leads to the activation of local cells (endothelial cells, fibroblasts, macrophages, epithelial cells, chondrocytes, osteoblasts, osteoclasts). The key cytokines in this process are the regulatory IL-23 and the effector IL-17 and IL-22, which mediate inflammation of the attachment sites and surrounding soft tissues (enthesitis, dactylitis), activation and inflammation of the synovial membrane (synovitis), as well as erosions, reactive-reparative changes, localized new bone formation, and systemic bone loss in and around the joints.

3.1.2. Symptoms and diagnosis

PsA is classified in the group of spondylarthropathies. Its most important features are synovitis with a polymorphic appearance, inflammation of tendon attachment sites (enthesitis) outside the joints, the appearance of sausage finger (dactylitis), a high frequency of extraarticular manifestations (most often skin, gastrointestinal, ophthalmic), and the typical radiological picture (sacroileitis, erosions with coarse reparative changes, flaky periostitis, formation of syndesmophyte and parasyndesmophyte in the spine). Up to 60% of patients develop progressive, erosive, deforming joint damage. Arthritis with very severe deformity (arthritis mutilans) affects approximately 5% of patients with PsA.

According to the oldest diagnostic/classification criteria system described by Moll and Wright in 1973, which is still used in many places today, PsA can be diagnosed in a patient with rheumatoid factor (RF) negative psoriasis if it is characterized by at least one of the following five clinical symptoms:

1) oligoarthritis (<5 pressure-sensitive and swollen joints) with an asymmetric appearance
2) polyarticular arthritis
3) DIP (distal interphalangeal) joint involvement
4) spondylitis
5) arthritis mutilans

Since then, several classification criteria systems have been developed, with the CASPAR (Classification of Psoriatic Arthritis study group) criteria being the most widely used.

3.1.3. Association between psoriatic arthritis and osteoporosis

Generalized bone loss can also be observed in inflammatory arthritis, such as psoriatic arthritis, but local reparative bone formation that takes place in parallel is also among the characteristics of the disease. Its various clinical manifestations include the formation of coarse osteophytes, the formation of enthesophytes, syndesmophytes and often bony ankylosis of the joints, especially the small joints of the spine. In addition to the loss and structural deterioration of the trabecular tissue, the cortical tissue decrease in volumetric BMD can also be consistently detected in a significant proportion of PsA patients.

The fundamental mechanisms of bone loss in inflammatory rheumatological conditions, including PsA, are essentially the same as those in rheumatoid arthritis (RA) and other autoimmune diseases. Proinflammatory cytokines play a central role, notably TNF-α and IL-17, which are also involved in the pathogenesis of osteoporosis. These cytokines enhance the production and surface expression of RANKL, which is crucial for osteoclast differentiation and activation. RANKL is expressed on peripheral lymphocytes, synovial membrane cells, and osteoblasts, leading to increased osteoclast activity and subsequent localized and systemic bone loss.

Certain proinflammatory cytokines (TNF-α, IL-1, IL-6) not only enhance bone resorption but also inhibit the differentiation, proliferation, and function of osteoblasts from mesenchymal stem cells. These cytokines, particularly TNF-α, interfere with the effects of IGF-1, RUNX2, and its downstream molecule, osterix (OSX). As a result, osteoblast differentiation and proliferation are inhibited. An indirect indication of the pathogenic role of the RANK-RANKL system, TNF-α, and IL-17 in bone loss is the significant BMD-increasing effect of RANKL-neutralizing antibodies in osteoporosis. The anti-osteoporotic effects of TNF antagonists have been described in

various inflammatory arthropathies and spondylarthritides, and similar effects of IL-17 inhibitors have been noted in spondylarthritis animal models.

In PsA patients, other factors that enhance bone remodeling also predispose to decreased bone density. These include inadequate vitamin D3 levels, inactivity due to functional decline, and resultant sarcopenia, where the effects of proinflammatory cytokines (IL-1, IL-6, IL-12, IL-17, TNF-α), medications used, immobility, and inadequate vitamin D3 levels play a central role.

Numerous studies and meta-analyses indicate that the likelihood of decreased bone density is significantly higher in PsA patients compared to non-PsA populations. The fracture risk in PsA patients exceeds the age- and gender-matched average for all types of fractures. This excess risk is only partially associated with decreased bone density, highlighting the importance of factors beyond bone density.

3.2. Objectives

In our study, we sought answers to the following questions:

1. Is there a difference in bone density, fracture risk, and the frequency of prevalent fractures and falls between patients with PsA and age- and gender-matched controls without PsA?
2. How do various disease-specific characteristics of PsA affect BMD, fall frequency, and the prevalence of fractures?

3.3. Patients and methods

We conducted an observational cohort study involving 61 patients with PsA and 69 randomly selected control patients, all under the care of the Rheumatology and Immunology Clinic at the Kenézy Gyula Campus of the University of Debrecen Clinical Center. The study was conducted from September 2021 to March 2022.

Patients diagnosed with psoriatic arthritis according to the CASPAR classification criteria were included, along with age-matched controls without PsA.

We excluded all patients who had other inflammatory arthritis (such as rheumatoid arthritis , systemic autoimmune diseases, or other spondyloarthritis); who had other underlying diseases affecting bone metabolism (such as primary hyperparathyroidism, thyroid diseases, kidney failure, malabsorption, alcoholism); who have received medical therapy affecting bone balance for more than 3 months, including corticosteroid therapy exceeding a dose of 5 mg , thyroid hormone replacement, or estrogen/androgen replacement therapy.

In the control group, we randomly selected patients from among those who were referred to our clinic by their general practitioner for osteoporosis screening, and who did not meet the exclusion criteria. The patients of both groups agreed to the use of their data for scientific purposes.

Based on the above, we reviewed the medical documentation of eligible patients, conducted interviews, and recorded the following data: clinical baseline data, alcohol consumption habits, smoking, fall risk factors (such as vision problems, balance disorders, dementia), history of previous fractures, number of falls in the past year, and DEXA scan results.

After the data recording, a physical examination was performed in the PsA patient group, and the disease-specific characteristics of PsA were recorded. These were the onset of psoriasis, duration, type (early or

late onset), type of skin lesions (plaque or guttate) and extent (BSA), involvement of the scalp, flexures or nails, type of PsA (peripheral or axial), the presence of enthesitis and/or dactylitis, and the therapy used. Based on the recommendations, we considered early-onset psoriasis if the symptoms appeared before the age of 40, and late-onset if after the age of 40. Flexural involvement included skin symptoms in the following areas: axilla, umbilicus, groin, perianal area, intergluteal cleft, and, in women, the area beneath the breasts. In cases of axial involvement, disease activity was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and peripheral involvement was assessed using the three-variable Disease Activity Score (DAS28).

Bone density was measured at the lumbar spine and the left femoral neck using a Lunar Prodigy densitometer (GE Healthcare Holding LLC) according to the manufacturer's recommended protocol. In cases of prior hip fracture or severe joint deformity or destruction, measurements were taken at the right femoral neck. The 10-year fracture risk was calculated using the FRAX tool.

Statistical analysis

For statistical analysis, we used IBM SPSS Statistics for Windows software (version 27.0, SPSS). Normality was assessed using the Shapiro-Wilk test. Continuous variable values between the two groups were compared using either the Student's t-test or the nonparametric Mann–Whitney U test. The Fisher's exact test and the chi-square test (κ^2) were used to examine associations between nominal variables, while the Kendall tau test was applied for ordinal variables. Significant predictors of binary outcome variables (such as disease type, osteopenia, or osteoporosis) were identified using stepwise logistic regression, and predictors associated with the number of fractures or falls were analyzed using ordinal regression.

3.4. Results

Comparison of PsA and control group

Among the patients, 3 had predominantly axial PsA, while 58 had predominantly peripheral PsA. The former received non-steroidal anti-inflammatory drug (NSAID) treatment, whereas the latter were treated with disease-modifying antirheumatic drugs (DMARDs), including methotrexate (34 patients), leflunomide (6 patients), sulfasalazine (4 patients), cyclosporine (1 patient), or azathioprine (1 patient). Additionally, 15 patients received a combination DMARD therapy (methotrexate-sulfasalazine).

Biologic therapy was administered to 3 patients with axial PsA (infliximab, etanercept, adalimumab) and to 11 patients with peripheral PsA (adalimumab - 4 patients, etanercept - 3 patients, secukinumab - 2 patients, infliximab - 2 patients). The median disease duration for PsA was 10 (7-17.5) months, and for skin symptoms, it was 17 (11-33) months. Currently, 35 patients had skin symptoms; 3 had guttate psoriasis, while the remaining patients had plaque psoriasis. Of the patients, 34 had late-onset psoriasis (after age 40) and 27 had early-onset psoriasis (before age 40).

Before investigating the primary endpoints, we compared the two groups in terms of factors relevant to bone loss and fracture risk. There was no significant difference between the two groups in terms of age (two-sample t-test: $p > 0.1$), BMI (Mann–Whitney test: $p > 0.1$), and fall risk factors (Fisher's exact test: $p > 0.1$). However, the proportion of men was significantly higher in the PsA group (25/61) compared to the control group (7/69) (Fisher's exact test: $p < 0.0001$). In the PsA group, the male-to-female ratio was nearly equal, consistent

with the typical distribution for PsA, whereas the control group had a female predominance representative of the average population sent for osteoporosis screening.

When the comparison between PsA and controls was limited to female patients, we found almost the same significant differences as for the whole group. Compared to controls, regular but not excessive alcohol consumption (maximum 1-2 units per day), corticosteroid therapy or continuous use of proton pump inhibitors were more common in the PsA group (Fisher test: p=0.046, p=0.0004 and p= 0.0006). However, these differences were not found to be independent influencing factors for the variables examined, according to statistical analysis (stepwise logistic regression and ordinal regression: $p > 0.1$).

BMD values measured on the lumbar spine showed no significant difference between the two groups (Mann– Whitney, $p > 0.1$). However, the BMD values measured at the femoral neck and the spine and femoral neck T- score values were significantly lower in the PsA group than in the control group (Mann- Whitney test: p=0.0029, p = 0.0002 and p< 0.0001). In the overall study population, decreased bone density was associated with the presence of PsA and was inversely related to BMI (logistic regression: $p < 0.0001$ and $p = 0.0026$). Osteopenia or osteoporosis was significantly more common in the PsA group compared to the control group (Fisher's test: $p < 0.001$). The odds ratio (OR) for osteopenia or osteoporosis in PsA versus control patients was 21.9 (CI 7.1–67.7); for the femur neck, 37.0 (CI 8.3–164.6); and for the spine, 12.9 (CI 2.8–58.8).

The 10-year fracture risk calculated using FRAX showed no significant difference between the two groups regarding the risk of major osteoporotic fractures (Mann– Whitney , $p > 0.1$). In contrast, the ten-year hip fracture risk was significantly higher in the PsA group (Mann– Whitney, $p = 0.014$).

Regarding the number of prevalent fractures, the PsA group had a significantly higher incidence of fractures compared to the control group, with 16 cases having multiple fractures, 10 with a single fracture, and 29 with no fractures, compared to 3, 10, and 56 cases respectively in the control group (Kendall tau: $p < 0.001$). The fracture prevalence of the control group did not differ from the average population of a similar age. The number of peripheral fractures (38 vs. 17) and vertebral fractures (16 vs. 4) was significantly higher in the PsA group than in the control group (Mann– Whitney test for distribution of fracture numbers, $p = 0.024$, $p = 0.0029$). For PsA patients, the odds ratio (OR) for overall fracture was 3.42 (CI: 1.56–7.52, $p = 0.002$), for peripheral fractures was 2.26 (CI: 1.01–5.04, p =0.048), and for vertebral fractures the OR was 13.33 (CI: 1.65–107, p=0.003).

The number of falls in the PsA group was significantly higher than in the control group (34 vs. 7, $p <0.001$). The odds ratio for falls in PsA patients compared to the control group was 3.95, indicating that PsA patients are approximately four times more likely to fall than those in the control group (CI: 1.17–13.27, Fisher's exact test: $p = 0.0018$).

BMD, fracture risk, factors associated with prevalent fractures and fall risk within the PsA group

No significant correlation was found between BMD, fracture risk and disease-specific characteristics of PsA. Ordinal regression analysis showed that (in addition to age) the number of frequent fractures was significantly associated with scalp involvement ($p = 0.0049$) and the late type of psoriasis ($p = 0.029$).

In the PsA group, the number of falls was significantly related to the late onset of psoriasis (ordinal regression analysis, $p = 0.0073$), as well as to the psoriasis involvement of body folds. ($p = 0.023$).

3.5. Discussion

The relationship between psoriasis and bone loss has been explored in numerous studies, often yielding contradictory findings. The large HUNT (Trøndelag Health Study) found that patients with only skin symptoms of psoriasis did not have a higher risk of increased bone loss or fractures compared to the general population without psoriasis. In contrast, Attia et al. observed that decreased bone density is more common in patients with PsA than in those with only psoriatic skin symptoms. A meta-analysis published in 2016, which reviewed data from 21 studies, found that 13 of these studies supported the notion of increased bone loss in PsA patients. Furthermore, Kathuria et al., through an analysis of insurance data encompassing over 183 000 psoriasis patients—including 28 000 with PsA—demonstrated that both psoriasis and PsA predispose individuals to osteopenia, osteoporosis, and low-impact fractures. A recent meta-analysis reached the conclusion that neither psoriasis nor PsA alone is associated with a heightened risk of osteoporosis. However, it did find significantly higher rates of low-impact fractures, underscoring that BMD is just one of several factors influencing fracture risk. These varying results indicate that the connection between psoriasis, PsA, and bone loss involves complex interactions, with BMD being only one aspect of the overall fracture risk profile.

Our results align with the findings of Kathuria et al., showing that osteopenia and osteoporosis are significantly more prevalent among PsA patients, both in the spine and at the femoral neck (Fisher exact test, $p < 0.001$) (OR 12.9 and OR 37). While the fracture risk calculated using FRAX did not reveal a difference in the risk of major osteoporotic fractures ($p > 0.1$), the risk of hip fractures was significantly higher ($p = 0.0005$) in the PsA group compared to the control group.Few data are available in the literature on the correlation between specific features of PsA and bone fractures. According to a recently published meta-analysis, PsA patients have a significantly higher chance of suffering a vertebral fracture (OR 2.09). Accordingly, we also found a significantly higher chance of suffering peripheral and vertebral fractures among our PsA patients (OR 2.26 and OR 13.33).

Our study also confirmed the results of Paskins et al., who found a 10% higher fracture risk in patients with late-onset psoriasis compared to age- and sex-matched controls. In our study, late-onset psoriasis and scalp involvement were also associated with increased fracture risk ($p = 0.029$ and $p = 0.0049$).

The relationship between annual fall frequency and PsA has been explored by only one research group. Their recent study describes an increased fall risk associated with joint involvement in the feet among PsA patients. We also observed a significantly higher number of falls in patients with late-onset psoriasis and psoriatic involvement of body folds ($p = 0.0073$ and $p = 0.023$).

One of our most interesting findings, that psoriatic involvement of the scalp and body folds increased the risk of fractures and falls, is similarly difficult to explain as why several features such as scalp lesions, nail dystrophy, and body fold lesions (most notably scalp lesions) increase the risk of PsA in patients with psoriasis. Some authors have observed that those patients with scalp involvement have more severe arthritis of the fingers and lower limbs, but similar observations have not been made for body fold involvement.

In the search for possible mechanisms, it has been shown that increased fall risk is observed in patients with rheumatoid arthritis, and by analogy, it is reasonable to assume that PsA may also contribute to fatigue, reduced movement function, muscle mass, mobility, and gait stability—all of which can impair mechanisms to prevent falls. Additionally, there is sporadic data suggesting that enthesitis in the lower limbs may alter foot mobility and gait patterns.

To our knowledge, this is the first study to assess the relationship between PsA-specific characteristics and bone fractures as well as falls. Our findings indicate that PsA predisposes individuals to reduced bone density, falls, and related fractures. Therefore, regular monitoring of BMD and the initiation of primary prevention should be considered for patients with PsA. Patients with late-onset psoriasis are at particularly high risk for falls and low-energy fractures, especially if the scalp and body folds have ever been involved or are currently affected. Accordingly, preventing falls and fractures requires special attention. This underscores the importance of collaboration between dermatologists and rheumatologists, which is essential for the comprehensive and successful management of PsA patients.

Limitations of our study

One limitation of our study is the small sample size and the study's singular central location. Additionally, the proportion of men in the PsA group was higher than in the controls, but gender alone did not prove to be a significant influencing factor for the variables examined in the statistical analysis. The gender distribution among PsA patients was more balanced, in contrast to the female predominance in the osteoporosis screening referrals, making it challenging to create a control group matched for age and gender. However, we believe that the results of our study are valid and highlight important new associations between PsA and osteoporosis.

4. SUMMARY, THE PRACTICAL SIGNIFICANCE OF THE RESULTS

In my work, I examined two aspects of osteoporosis that are important from a practical standpoint. The first of these is the enhancement of therapy adherence among osteoporotic patients in rheumatological practice by adapting treatment strategies accepted in the management of other diseases, such as tight control and the treat-to-target strategy. Today, obstacle to the effective treatment of osteoporosis is not the lack of effective medications, but the inadequate adherence of patients, which clinically results in less BMD gain, higher fracture, and mortality risk. Various attempts have been made to improve this, including patient education and follow-up strategies, as well as changes in the dosing intervals and methods of drug administration. These efforts have led to some improvements in the case of parenteral agents, but no significant breakthrough has been achieved with the more commonly used oral medications. The use of a therapeutic strategy that includes treating the reduction in bone turnover markers as a target value and making therapy decisions based on the BMT levels, along with close patient monitoring, could be a breakthrough in improving adherence and, consequently, increasing the effectiveness of therapy.

Osteoporosis associated with inflammatory rheumatologic diseases (primarily RA) was not unfamiliar to practicing rheumatologists. However, it is less well known that patients with psoriasis and PsA are also at risk for decreased bone density and, consequently, an increased risk of fractures. At the same time, we did not have data on whether PsA patients are at elevated risk for falls, which is one of the most important fracture risk factors. There are no data in the literature on the relationship between the specific manifestations of PsA and the risk of fractures and falls. To our knowledge, this is the first study to find a correlation not only between bone mass but also between fractures, falls, and PsA. Additionally, we were the first to describe the significance of PsA-specific disease characteristics. Our results suggest that patients with late-onset psoriasis are at particularly high risk for

falls and low-energy fractures, especially when the scalp and body folds are involved. From a practical perspective, this means that even within the PsA population, a specific patient group needs to be highlighted, for whom early densitometric screening, management, and treatment are of particular importance for primary fracture prevention.

5. NEW RESULTS

For the first time, we examined the impact of a treatment strategy based on tight control and bone turnover markers as target values on BMD increase. According to our results, the BMD increase measured at the femoral neck in patients treated based on tight control and target values was significantly greater than in patients who visited the clinic only annually. Therefore, this treatment strategy also has justification in osteoporosis. Furthermore, we found significantly better compliance in the tight control group with vitamin D3, calcium, and oral bisphosphonates.

Our second study was the first in the literature to investigate the relationship between PsA-specific characteristics and falls and fractures, and to compare the frequency of falls and fractures as well as fracture risk between patients with and without PsA. Our findings confirmed that PsA increases the risk of developing osteoporosis, while also showing that fall and fracture risks were elevated among PsA patients. We identified associations between certain disease-specific factors and fall and fracture risks. We found that late disease onset and joint involvement increased fracture risk, while late disease onset and scalp involvement increased fall risk. Based on these findings, a subgroup of PsA patients with increased fall and fracture risks can be identified, who deserve special attention for early osteoporosis screening and treatment.

6. KEYWORDS

Keywords: osteoporosis, fracture risk, psoriatic arthritis, risk of falls, tight control, prevention of fractures

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8. APPENDIX

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List of publications related to the dissertation

1. **Halasi, A.**, Szegedi, A., Töröcsik, D., Varga, J., Farmasi, N., Szűcs, G., Tarr, T., Gaál, J.: Psoriatic arthritis and its special features predispose not only for osteoporosis but also for fractures and falls.
   J. Dermatol. 50 (5), 608-614, 2023.
   DOI: http://dx.doi.org/10.1111/1346-8138.16710
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2. **Halasi, A.**, Kincse, G., Varga, J., Kéri, J., Gaál, J.: Tight control: a new therapeutic strategy in the management of osteoporotic patients.
   Osteoporosis Int. 29 (12), 2677-2683, 2018.
   DOI: http://dx.doi.org/10.1007/s00198-018-4674-7
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List of other publications

3. **Halasi, A.**, Gaál, J.: A parenterális antiporotikus szerek adherenciájának kérdései a szekunder prevenció tükrében.
   Osteol. Közl. 32 (1-2), 20-23, 2024.

4. Farkas, R., Varga, J., **Halasi, A.**, Szűcs, G., Gaál, J.: A reumatológiai betegségek célzott terápiáinak perzisztenciáját befolyásoló tényezők vizsgálata.
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7. **Halasi, A.**, Kincse, G., Varga, J., Gaál, J.: Orális biszfoszfonátok perzisztenciája - real life adatok egy debreceni centrumból.
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